

A Double-Blind, Randomized, Placebo-Controlled Study of Tolcapone for OCD

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Protocol Title: A Double-Blind, Randomized, Placebo-Controlled Study of Tolcapone for OCD

This project will take place at the University of Chicago. Dr. Jon E. Grant, MD, JD is the Principal Investigator and can be phoned at 773-834-1325 or reached by email at jgrant4@bsd.uchicago.edu.

This clinical trial will be conducted in the spirit of Good Clinical Practice and in accordance with this IRB approved protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

Investigational Agent and Dosing:

Tolcapone 100mg to 200mg taken orally twice daily

Population:

The population to be studied for this trial is 85 men and women ages 18-65 who have a current, primary diagnosis DSM-5 diagnosis of moderate to severe obsessive compulsive disorder (OCD).

Project Goals:

The primary aim of the present study is to examine the efficacy and safety of tolcapone in adults with moderate to severe OCD. Subjects will receive 8 weeks of double-blind tolcapone or placebo. The hypothesis to be tested is that tolcapone will significantly improve symptoms of OCD compared to placebo.

Background:

Current first-line treatments for OCD include cognitive behavioral therapy using exposure and response prevention, or serotonin reuptake inhibitors (SRIs) (Skapinakis et al., 2016). While helpful for many, not everyone can tolerate these interventions (e.g. SRIs often have intolerable sexual side effects), or find trained therapists, and up to 35% of people do not experience adequate symptom relief (Grant, 2014).

Tolcapone, a catechol-O-methyl-transferase (COMT) inhibitor, is used in some countries (including the UK and USA) as an add-on agent for the management of Parkinson's Disease. The

enzyme COMT serves to break down free dopamine in the prefrontal cortex; by blocking this enzyme, tolcapone enhances dopamine signaling in the cortex. In the frontal cortex, optimal dopamine modulation of prefrontal cortical networks is necessary for a variety of cognitive functions, including planning, inhibition, attention, and response flexibility (Tunbridge et al., 2004). Importantly, dysfunction of many of these cognitive domains has been implicated in OCD (Chamberlain et al., 2005).

We recently conducted a proof of concept pilot study using tolcapone in patients with OCD using a double-blind, cross-over two-week design (Grant et al., 2021). Two weeks of tolcapone was associated with significant improvement in OCD versus two weeks of placebo ($t=2.194$, $p=0.0409$). The mean percentage decreases in total symptom severity scores for the entire sample over the corresponding two-week periods were 16.4% for tolcapone and 3.6% for placebo. These data strongly support the need for formal treatment trial of appropriate sample size and duration to characterize the efficacy of tolcapone in OCD.

Primary Aim/Objective:

Based on the mechanism of action and our previous pilot data, the primary aim of the present study is to examine the efficacy and safety of 8-week treatment with tolcapone vs. placebo in adults with moderate to severe OCD, as indicated by a score of at least 21 on the *Yale Brown Obsessive Compulsive Scale* (YBOCS), a scale of illness severity, at the baseline visit. We hypothesize that tolcapone will significantly improve symptoms of OCD compared to placebo.

Primary Endpoint:

The primary efficacy measure will be the change in severity of OCD symptoms as indicated by the change in total score from Baseline to week 8 on the YBOCS.

Secondary Aims/Objectives:

A secondary aim of the proposed study is to examine the cognitive effects of tolcapone in OCD, by conducting objective neuropsychological tasks pre- and post-pharmacological trial. The rationale for this approach is that: dopamine plays a key role in cognition; cognitive effects of tolcapone are likely to be relevant in explaining symptomatic effects; and cognitive dysfunction constitutes an important treatment target in OCD that is not generally ameliorated by current first-line interventions. We hypothesize that any symptomatic benefit with tolcapone would also be associated with improvement in executive functions including cognitive flexibility.

Another secondary aim of the proposed study is to evaluate whether the single nucleotide polymorphism (SNP) Val-158-Met polymorphism significantly relates to changes in symptoms and cognition observed with tolcapone. Prior data indicate cognitive effects of tolcapone are affected by this SNP. We hypothesize that the val/val COMT variant will be associated with significantly higher tolcapone-related improvements in cognition and symptoms, since this is linked to lower cortical dopamine function.

Another secondary aim is to examine the effects of tolcapone vs placebo on measures of mood and quality of life.

Secondary Endpoints:

Secondary efficacy measures include changes in CANTAB cognitive assessment, Quality of Life Inventory, and The Montgomery-Åsberg Depression Rating (MADRS) scores from baseline to week 8.

Methodology:

85 individuals with OCD will be recruited for a parallel, double-blind, randomized placebo-controlled study in which tolcapone or placebo is administered in a 1:1 fashion. All 85 participants will have current OCD per DSM-5 criteria. Following baseline measures, subjects will receive tolcapone (initially 100mg twice per day) or inactive placebo. Dose will be increased, if tolerated, from 100mg twice daily to 200mg twice daily at week 2. Participants will be seen every 2 weeks during the 8-week period. At week 8, subjects will start a 1-week taper off the medication. Efficacy and safety measures will be performed at each visit.

The study will be conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, all local ethical and legal requirements, and the World Medical Assembly (Declaration of Helsinki). The study protocol and procedures will be approved by the University of Chicago's institutional review board prior to any recruitment. Written informed consent will be required for study participation.

Randomization of drug will be conducted in blocks of eight. In event of an emergency, the blind will be assessable to the study subject by calling the pharmacy number listed on the medication bottle. In this event, the study subject will be discontinued from the medication, and a safety follow-up visit will be scheduled one week following discontinuation. The study subject will not know what arm of the study they are on otherwise. The investigational pharmacy will follow proper accountability procedures in regards to both randomization of the study drug and holding of the blind.

Subjects:

Inclusion Criteria:

- 1) Men and women age 18-65 years
- 2) Primary diagnosis of OCD
- 3) YBOCS score of at least 21 at baseline (moderate or higher severity)
- 4) Ability to understand and sign the consent form

Exclusion Criteria:

- 1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination
- 2) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential
- 3) Subjects considered an immediate suicide risk based on the Columbia Suicide Severity rating Scale (C-SSRS) (www.cssrs.columbia.edu/docs)
- 4) History of psychosis or bipolar disorder based on DSM-5 criteria
- 5) Alcohol/substance use disorder and/or illegal substance use based on urine toxicology
- 6) Initiation of psychological interventions within 3 months of screening (those who are continuing with CBT will be included)

- 7) Use of any new psychotropic medication within 3 months of study entry (stable doses of psychotropics will be allowed)
- 8) Major cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent
- 9) Abnormal liver function tests at baseline (greater than 2x the upper limit of normal)
- 10) MADRS ≥ 30 at baseline

Subject Recruitment:

Subjects will be identified through advertisements posted in the Chicagoland area (flyers, social media advertisements) and from referrals from clinicians in the community. Advertisements will require interested participants to contact the study staff or complete a brief pre-screening to provide their contact information. Study staff will call interested subjects and complete a 5-10 minute phone screening to pre-assess their eligibility (based on the inclusion and exclusion criteria). No direct solicitation of potential subjects will be done by any of the research staff.

Baseline Assessments:

Subjects will be seen at baseline and then every two weeks during the 8-week treatment period. Those subjects who appear appropriate for the study, based on telephone screening, will be invited for a baseline assessment. The duration of the baseline assessment will be last between 90-120 minutes and will include the following: Informed consent, Demographic data, Concomitant medications, Family history data, Medical evaluation including physical examination, weight, and vital signs, Urine pregnancy test and urine drug screen, and a psychiatric evaluation. The COMT polymorphism will be quantified using a convenient saliva sample collected from participants.

Cognitive Assessments:

Assessments of cognitive control will be comprised of several valid paradigms (See below). These tasks are designed to probe dissociable neural circuitry and cognitive processes likely to be implicated in the pathophysiology of addictions. Task order was chosen arbitrarily and will be applied consistently across subjects, to minimize possible confounding factors of differences in task order across participants.

The following tasks will be administered at baseline and final visits:

- Stop Signal Task of Inhibitory Control (SST)
- Intra-dimensional/Extra-dimensional Set Shift Task (ID/ED task)
- One Touch Stockings Task (OTS)
- Rapid Visual Processing Task (RVP)
- Spatial Working Memory Task (SWM)
- Cambridge Gambling Task (CGT)

Follow-Up Visit Assessments:

This is a 9-week study (8 weeks of acute treatment followed by a 1-week tapering phase). Subjects will be seen at baseline and then every two weeks during the 8-week treatment period. Week 6, and Week 9 visits will be completed virtually via hospital-encrypted Zoom calls. Virtual visits will take approximately 30 minutes, and in-clinic follow-up visits will take approximately

60-90 minutes. See the schedule of activities on following page for the assessments to be completed at each visit.

Schedule of Activities

	Baseline (Visit 1) In Clinic	Week 2 (Visit 2) In Clinic	Week 4 (Visit 3) In Clinic	Week 6 (Visit 4) Virtual	Week 8 (Visit 5) In Clinic	Week 9 (Visit 6) Virtual
Informed Consent	X					
Concomitant Medications	X	X	X	X	X	X
Demographic Data	X					
Family History Data	X					
Clinical Intake Interview	X					
Physical Examination	X					
Weight Measurement	X				X	
Vital Signs (BP, temp, pulse, respiratory rate)	X		X		X	
Urine Pregnancy Test (for WOCBP)	X					
Urine Drug Screen	X					
Saliva Sample Collection	X					
Liver Functioning Tests (ALT & AST)	X	X	X		X	
YBOCS	X		X		X	
MADRS	X		X		X	
C-SSRS	X	X	X	X	X	X
Quality of Life Inventory	X				X	
CANTAB Cognitive Testing	X				X	
Randomization (1:1)	X					
Adverse Events Assessment	X	X	X	X	X	X
Dispense Drug	X		X			

Subject Compensation:

Subjects will be compensated \$25 per visit, for a total of \$150 if all study visits are completed. Compensation will be given in the form of a check at the end of the study, as per University of Chicago protocol.

Subject Withdrawal:

If a subject withdraws from the study, all instruments administered at the screening visit will be completed at the final visit. These will be conducted when the subject is able to come in for an early termination visit. Withdrawn subjects will be given the phone number of the principal investigator as well as the phone numbers of local resources for OCD treatment.

Subject Termination:

If a subject fails to take the medication for a consecutive three-day period or fails to attend weekly visits, they will be terminated from the study. In this case, the procedures for Subject Withdrawal will be followed (see above).

Safety Assessments:

Safety and tolerability will be assessed using spontaneously reported adverse events data, Columbia–Suicide Severity Rating Scale (C-SSRS), vital signs, and by evaluating premature termination. C-SSRS, adverse events, and concomitant medications will be documented at all visits. Sitting blood pressure and heart rate will be documented at all in-clinic visits. Subjects who are an immediate suicide risk will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. Urine pregnancy tests will be performed at the initial visit. Subjects who have a positive urine pregnancy test will be excluded from the study. Assessment of side effects will be done at each visit. AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (Med- DRA) Version 11.1. The incidences of all AEs will be summarized descriptively. In terms of vital signs, those subjects with abnormal blood pressures will be assessed for symptoms of hypo- or hypertension. Asymptomatic subjects will be evaluated each visit for changes in vital signs. In the case of hypertensive emergencies (BP greater than 210/120), appropriate referral to the emergency room will be made. In the case of hypotension (BP less than 90/60), participants will be evaluated for symptoms of hypotension and if symptomatic, appropriate interventions will be made.

Adverse Event Reporting:

Unanticipated (unexpected) problems/events, those that are not already described as potential risks in the consent form, or not part of an underlying disease, will be reported to the IRB as soon as possible. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

Risks:

Participants may experience side effects while taking the drugs used in this study. Side effects are usually reversible when the drug is stopped but occasionally continue and may cause serious

complications, if subjects experience any side effects, they will be asked to contact the study doctor immediately.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence their willingness to continue, this new information will be discussed with the participant.

Risks of Tolcapone

Tolcapone has been associated with hepatic failure in some individuals and carries a Black Box warning of hepatotoxicity from the FDA. Given the total daily tolcapone dose of 400mg/day used in this study is lower than the 600mg/day dose used in Parkinson's disease and the dose associated with hepatotoxicity. We feel that the risk of hepatotoxicity is very low. Hepatotoxicity associated with tolcapone has been documented when the medication has been used continuously for at least 16 weeks at total daily doses of 600mg/day and liver function tests were not monitored.

Patients will also be assessed for clinical signs of hepatic dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, and pruritus), and liver functioning tests (ALT and AST) will be collected at baseline, week 4, and week 8.

Other common adverse events associated with tolcapone (nausea, diarrhea, orthostatic hypotension, somnolence, confusion, hallucinations, and rhabdomyolysis) are possible, and will be monitored.

Risks of blood draws

Needle sticks can cause discomfort, pain, burning sensation or bruising.

Incidental Findings:

There are no possibilities for incidental findings as a result of this research.

Data Analysis:

Data analysis will involve all visits during the 8-week double-blind treatment phase (up until week 8). Data from the tapering phase (weeks 8-9), although collected, will not be included for purposes of the primary goal of this study.

All enrolled participants will be included in the analyses of baseline demographics and safety according to an intent-to-treat (ITT) principle. For statistical analysis, the full-analysis set will be defined as all participants who took at least 1 dose of the study drug and had at least 1 post-baseline primary efficacy assessment. The safety-analysis set will be defined as all randomized participants who took at least 1 dose of the study drug and completed at least 1 follow-up safety assessment. The statistical model will be a rigorous linear mixed-effects regression model (LME) that includes terms for treatment group, time, and treatment-by-time interaction. The analyses will run using the nlme package on R for Windows. Literature suggests LME without imputation may provide more accurate and stable results than LME models using fixed and multiple imputation methods for handling missing data. All tests of hypotheses will be performed using a two-sided significance level of 0.05.

Data Handling and Record Keeping:

All subject data will be maintained by the study personnel under the supervision of the principal investigator. Subjects will be seen at the University of Chicago. All study recording, including patient binders, will be kept in a locked room in that is only accessible to research staff within the Department of Psychiatry. Data may be entered electronically on an encrypted, password-protected data entry application (REDCap). Data will not be shared with other University of Chicago investigators or with investigators outside of the University of Chicago.

At study termination, data will be kept indefinitely in locked cabinets in a locked room only accessible to research staff within the Department of Psychiatry. If there is a data breach at the University of Chicago, research staff will contact the IRB and HIPAA Office as soon as possible to report the problem. All University of Chicago guidelines for data breaches will be followed.

Data Safety and Monitoring Plan:*1) Responsibility for Data and Safety Monitoring*

- a. The PI will have overall responsibility for monitoring the integrity of study data and participant safety.

2) Procedures for Monitoring Participant Safety

- a. The PI will implement the following procedures to ensure data integrity and the safety of participants during the study.
 - A number of elements of the research plan are intended to minimize the risks of study participation. If subjects become actively suicidal with intent and plan to kill themselves, the PI will evaluate them and refer them for immediate non-study treatment. Any participant endorsing suicidal thoughts with intent and plan will be immediately evaluated by the PI and referred to a higher level of care if clinically indicated.
 - The PI will evaluate patient safety and resolve any safety issues if necessary, as such issues arise. The PI will also be responsible for preparing written summary reports of adverse events and will prepare a written report summarizing any decisions that are made pertaining to participant disposition.
 - Data integrity and confidentiality will be safeguarded as discussed in the above Data Analysis and Data Handling and Record Keeping Section.

Monitoring Committee:

We will establish a monitoring committee and define in detail its role, its composition, and its operating procedures for reviewing patient safety and data from this study. The monitoring committee, comprised of two individuals independent of personnel involved in the study, including a psychiatrist and a statistician, will come together via conference call every 6 months. The committee will use a standardized approach employing contemporary bio statistical, psychiatric/psychological, and ethical principles to review study design and interim data. The committee will audit the records from the study and will ensure the data are being collected, managed and protected. The committee will have the ability to ask for more frequent reviews at any time if they deem it necessary. In addition, the PI will inform the committee of any serious adverse event.

The PI will prepare a specific report for the committee in advance of each meeting. Attention will be given to data quality and timeliness, recruitment, risk versus benefit, adverse events and other factors that could affect study outcome.

Reporting Adverse Events:

- Any serious adverse event will be reported to the Institutional Review Board (IRB) at the University of Chicago in a full written report within 10 working days of the event. For fatal/life-threatening serious adverse events, the PI will notify the IRB Chair by phone immediately.
- Any moderate adverse event which appears definitely, probably, or possibly related to study participation will be reported to the University of Chicago IRB in writing within 20 working days.
- Any mild adverse event will be summarized in the IRB annual progress reports.

Interim Efficacy Analysis:

Interim efficacy analysis may be performed if no improvements from the study drug are suspected.

Ethical Considerations:

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Chicago research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Chicago Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

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